PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK2004/000862	14.12.2004	15.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/135, A61K31/343, A61K31/454, A61K45/06, A61P25/24, A61P25/18

Applicant
H. LUNDBECK A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000862

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-24 (partially); 25

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-24 (partially); 25

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11,17
	No:	Claims	1-10,12-16,18-24
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III.

1. Present claim 25 encompasses a genus of compounds defined only by their function, namely a compound identified according to any of the claims 22-24, wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, no search has been performed for claim 25 (Articles 5 and 6 PCT).

2.1 Present claims 1-21 relate to a compound defined by reference to a desirable characteristic or property, namely the activities as: serotonin reuptake inhibitor and H3 receptor antagonist, inverse agonist or partial agonist.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds, namely the compounds of claims 10 and 11. In the present case, the claims so lack support, and the application so lacks disclosure. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).
An attempt is made to define the compounds by reference to their pharmacological profile, rendering the scope of protection obscure. It is pointed out that a compound cannot be sufficiently characterized by its pharmacological profile or its mode of action: such a definition is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).
Therefore, the search for claims 1-21 has been restricted to the combinations of the compounds of claim 10 together with the compounds of claim 11.

2.2 Concerning claims 22-24, the claims lack support and the application lacks disclosure. Since no example of tests to evaluate the activity of a compound as a serotonin reuptake

inhibitor or as a H3 receptor antagonist, inverse agonist or partial agonist, has been given, the application lacks any indication as to how it can be performed. This lack cannot be compensated by the skilled person endowed only with his common knowledge; it is for example impossible for the skilled person to test the biological activity of the claimed compounds, given the large number of possible *in vitro* tests and animal models which could in principle be used. It is concluded that the skilled person, in order to carry out the claimed subject-matter, would be forced to extensively consult the state of the art and furthermore use a lot of inventiveness in selecting the useful information extracted by this search in order to put the present invention into practice. This is taken as a proof that the application lacks disclosure (Article 5 PCT). Moreover, claims 22-24 lack support under Article 6 PCT.

3. No Opinion will be carried out in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).

Re Item V.

1. The applicant attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up (i.e. the compounds of claim 10 in combination with the compounds of claim 11 for treating the disorders of claim 1).

2. Reference is made to the following documents:

D1 : EP 0 966 967 A (ELI LILLY AND COMPANY) 29 December 1999 (1999-12-29)

D2 : WO 99/61027 A (ELI LILLY AND COMPANY; TOLLEFSON, GARY, DENNIS) 2 December 1999 (1999-12-02)

D3 : WO 99/20279 A (ELI LILLY AND COMPANY; PERRY, KENNETH, WAYNE) 29 April 1999 (1999-04-29)

D4: SCHLICKER E ET AL: "Effects of Imidazolines on noradrenaline release in brain: An investigation into their relationship to imidazoline, [alpha]2 and H3 receptors" NEUROCHEMISTRY INTERNATIONAL 1997 UNITED KINGDOM, vol. 30, no. 1, 1997, pages 73-83, XP008056901 ISSN: 0197-0186

D5: MORISSET S ET AL: "Atypical neuroleptics enhance histamine turnover in brain via 5-hydroxytryptamine2A receptor blockade" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 288, no. 2, February 1999 (1999-02), pages 590-596, XP008056904 ISSN: 0022-3565

D6: EP 0 978 512 A (SOCIETE CIVILE BIOPROJET) 9 February 2000 (2000-02-09)

Novelty

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-10,12-16,18-24 is not new in the sense of Article 33(2) PCT.

Document D1 discloses the use of fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, duloxetine, a serotonine reuptake inhibitor according to present claim 1, more specifically to claim 10, in combination with clozapine, a compound falling under the definition of present claim 1 of H3 receptor antagonist, (see document D5) for treating bipolar disorder, synonym of obsessive compulsive disorders, and compositions thereof.

Document D2 discloses the use of fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, duloxetine, a serotonine reuptake inhibitor according to present claim 1, more specifically to claim 10, in combination with clozapine, a compound falling under the definition of present claim 1 of H3 receptor antagonist, (see document D5) for treating depression, and compositions thereof.

Document D3 discloses the use of fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, duloxetine, a serotonine reuptake inhibitor according to present claim 1, more specifically to claim 10, in combination with moxonidine, a compound falling under the definition of present claim 1 of H3 receptor antagonist, (see document D4) for treating depression, and compositions thereof. The moxonidine potentiates the effect of the serotonine reuptake inhibitor.

The subject-matter of claims 1-10,12-16,18-24 is therefore not new over D1-D3 in the sense of Article 33(2) PCT.

3.2 Concerning the tests of claims 22-24, there are many well known tests in the art falling under the present definition: a test to measure of the ability of compounds to inhibit serotonin reuptake is commonly used in the art, as well as a test to measure of affinity of compounds at the H3 receptor. D4 and D5 disclose tests performed on compounds in order to evaluate their H3 receptor binding activity and their activity as H3 receptor antagonists. D3 describes a pharmacological tests to establish the serotonin reuptake activity as being standard tests well known in the art (see D3: page 7, paragraph 3).

The subject-matter of claims 22-24 is therefore not new over the prior art in the sense of

Article 33(2) PCT.

Inventive step

4.1 Concerning the coadministration of a serotonin reuptake inhibitor with a H3 receptor antagonist, inverse agonist or partial agonist, the attention of the applicant is drawn to the fact that the use of a combination of two or more active compounds having a already known activity, is to be considered as inventive only if it gives a proven surprising effect. The presently claimed serotonin reuptake inhibitors are already known as antidepressants, anxyolitics: see D1-D3. The presently claimed H3 receptor antagonists, inverse agonists or partial agonists are already known for treating depression and anxiety: see D6.

A synergisitc effect is necessary to motivate an inventive step for the use of a combination of two compounds individually known for the treatment of a disease: simple additive effects between fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, duloxetine and the H3 inhibitors of claim 11 can not serve as basis for inventivity.

It is pointed out that no synergistic effect has been proven by the Applicant. There are no examples showing that these combinations are really synergistic. In the absence of any evidence that the present compositions showed either an unexpected high synergetic effect or reduced side-effects, the presence of an Inventive step has to be denied. For establishing inventive step it is necessary to make credible, on the balance of probability, the existence of a true supra additive synergism, if, as in the present case, the combination of two known active compounds is prima facie obvious in view of their known properties. It would therefore be obvious to the person skilled in the art, to use for treating the disorders of claim 1 fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine, duloxetine, already known for treating depression, anxiety, obsessive compulsive disorders (see D1-D3), in combination with H3 receptor antagonists, inverse agonists or partial agonists, well known anti anxiety and antidepressant agents (see D6).

4.2 Concerning the tests of claims 22-24: D4 and D5 disclose tests performed on compounds in order to evaluate their H3 receptor binding activity and their activity as H3 receptor antagonists. D3 describes the pharmacological tests to establish the serotonin reuptake activity as standard tests well known in the art. It would be obvious for the man skilled in the art, to test the same compound using two tests chosen from well known assays, for its activity as serotonin reuptake inhibitor and as H3 receptor antagonist, inverse agonist or partial agonist.

Claims 1-24 lack therefore an inventive step under Article 33(3) PCT.